St John's wort versus paroxetine for depression

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Szegedi A, Kohnen R, Dienel A, Kieser M. Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St. John's wort): randomized controlled double blind non-inferiority trial versus paroxetine. *BMJ* 2005;330(7490):503. DOI: 10.1136/bmj.38356.655266.82.

Research question

How does St John's wort compare with paroxetine in terms of safety and efficacy for the treatment of moderate to severe depression in adults?

Type of article and design

Double-blind randomized controlled trial powered to test for non-inferiority of St John's wort versus paroxetine in 251 adult outpatients from 21 psychiatric primary care practices in Germany.

Relevance to family physicians

Depression was the fourth most common diagnosis made in Canada in 2006, and an increasing number of family physician visits are related to depression.[1] Canadian studies looking at lifetime incidences of major depression found that 7.9% to 8.6% of adults older than 18 years and living in the community met the criteria for a diagnosis of major depression at some time in their lives.[2] Furthermore, depression is associated with various disabilities, including cardiovascular disorders and diabetes.[3]

Most patients with major depression are treated by their family physicians, and an important component of treatment often is antidepressant medications. Numerous antidepressant agents of various pharmacological classes have established efficacy and other benefits in the treatment of depression. Types and frequencies of adverse events associated with their use vary.[4] Selective serotonin reuptake inhibitors (SSRIs), including paroxetine, accounted for 81% of all medication prescriptions dispensed for depression in 2003.[1] The use of herbal products in Canada has been increasing in the past decade, and results of recent studies suggest that more patients are turning to herbal medicines for the treatment of depression.[5]

St John's wort is commonly taken for depression,[6] and is considered by many people to be a safer and more natural alternative to standard antidepressants. Meta-analyses have shown that St John's wort is more effective than placebo in adults with mild to moderate depression. Results generated are comparable to standard antidepressants and show better tolerability.[7] Therefore, it is helpful to understand how St John's wort compares with standard antidepressant medications in terms of efficacy and safety in the treatment of moderate to severe depression.

Overview of study and outcomes

Two hundred fifty-one outpatients ranging from 18 to 70 years of age who experienced single or recurrent moderate or severe episodes of unipolar depression without psychotic features were recruited from 21 psychiatric primary care centres across Germany. Moderate to severe depression was defined as a score of at least 22 points on the 17-item Hamilton Depression scale (HAM-D) with a value of at least 2 scored for the item "depressive mood." The investigators included a run-in period that excluded patients who were early responders, noncompliant, or had refractory depression. Patients who met the inclusion criteria were randomized to 900 mg/d of St John's wort (*Hypericum* extract WS 5570) or 20 mg/d of paroxetine for 6 weeks. The doses of both agents were doubled for nonrespondents after 2 weeks.

Efficacy and safety were assessed at regular intervals by psychologists and psychiatrists who were trained before patient inclusion. The primary outcome measure was the absolute decrease of the HAM-D score between baseline and 6 weeks. Secondary outcome measures were the Montgomery-Åsburg Depression Rating Scale (MADRS), the Beck Depression Inventory (BDI), and the clinical global impressions. Psychiatrists and psychologists evaluated safety and tolerability based upon spontaneous reports of adverse events, a semistructured interview probing for known side effects of the treatments, routine laboratory measurements, and physical examinations.

Results

Efficacy. After 6 weeks of treatment, the HAM-D scores decreased by an average of 14.4 (SD 8.8) points (corresponding to 57% [SD 34%] of baseline value) for St John's wort and by 11.4 (SD 8.6) points (45% [SD 34%]) for paroxetine. St John's wort was at least as effective as paroxetine. Eighty-six of 122 patients (70%) from the St John's wort group and 73/122 (60%) from the paroxetine group demonstrated a response to their respective treatment (difference 11% [95% confidence interval (CI), 1%-23%]; $P=.08$). Response was defined as a decrease in score to at least 50% of their original baseline HAM-D score. Of those patients, 61/122 (50%) of the St John's wort and

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43/122 (35%) of the paroxetine patients showed remission (difference 25% [95% CI, 13%-37%] $P=.02$), defined as a decrease in HAM-D score to less than 10 points by week 6. The MADRS decreased by 16.4 (SD 10.7) for St John's wort and 12.6 (SD 10.6) for paroxetine ($P=.01$), and the BDI decreased by 10.2 (SD 10.3) and 7.0 (SD 9.3) ($P=.01$) for St John's wort and paroxetine, respectively.

Safety. During the 6-week treatment period, 69/125 (55%) patients randomly assigned to the St John's wort group reported 172 adverse events, and 96/126 (76%) of those in the paroxetine group reported 269 events. The incidence of adverse events for those treated with St John's wort was 0.035 events per day of exposure, whereas those treated with paroxetine experienced 0.060 events per day of exposure. The most commonly reported adverse events for St John's wort were dry mouth, fatigue, and headache, while dry mouth, dizziness, and diarrhea were the most commonly reported events for paroxetine.

Analysis of methodology

This was a well-designed, multicentre, randomized, double-blind, controlled trial. All aspects of study design (randomization, allocation concealment, blinding, intention-to-treat analysis, follow-up, inclusion and exclusion criteria, choice, definition, and assessment of outcomes) were adequately reported and met the standards for good-quality randomized controlled trials. The investigators stated that a non-inferiority trial using an active control group instead of a placebo group was conducted because it is generally considered unethical to treat severely depressed patients with placebo for 6 weeks. The research was funded by the manufacturers of the St John's wort extract used, and this was fully disclosed in the article.

The effect of choosing paroxetine as the comparator to St John's wort extract on adverse events is important to consider. Adverse events were more common in patients taking paroxetine than in those taking St John's wort extract, and more patients in the paroxetine arm discontinued study medication because of adverse events. Previous studies indicate that paroxetine might be associated with more adverse events than other SSRIs.[2,8] It is therefore possible that a smaller difference in adverse events might have occurred if another SSRI had been chosen as the comparator, in place of paroxetine.

There is considerable controversy over the use of placebo arms in randomized controlled trials for depression because patients receiving placebo often do as well as patients taking active treatment allowing for a better understanding of the context of response to therapy, as was found in the *Hypericum* Depression Trial Study Group where hypericum, sertraline, and placebo demonstrated similar improvement (and thus no difference over placebo).[9] The current study lacks the ability to determine whether either therapy is an improvement over placebo.

This study is primarily limited by its short duration of treatment and outcome evaluation. Because the trial is so short, this study could not assess some other important outcomes including recurrence rates, functional status, quality of life, or pharmacoeconomic impact. To do so, a larger study over a longer term would be required. The authors state that they will report the 4-month maintenance phase results of patients who responded to treatment. These results will be an improvement over the results of the 6-week trial but still fall short of the more recent regulatory requirements for new antidepressant medications that expect evidence for maintenance of efficacy up to at least 1 year.

Applications to clinical practice

As rate of herbal use grows, primary care physicians should be familiar with alternative treatments to traditional antidepressants. The study demonstrated that St John's wort (*Hypericum* extract WS 5570 300 mg 3 times daily) might be an alternative to paroxetine in treating adult patients for moderate to severe depression in the response phase of treatment; however, because longer-term studies are not available, it is unclear how longer-term improvements in depression as well as risk of relapse would differ between treatments. Currently, these results can be applied only to patients with unipolar moderate to severe depression without psychotic features. This could be a challenge for family physicians who see patients with a range of depression syndromes or comorbid psychiatric disorders because treatment decisions for people in this "gray area" are often difficult to make. In addition, these results might not be applicable to patients with refractory depression because these patients were excluded from the study.

Patients taking St John's wort experienced fewer side effects than those taking paroxetine. Reducing side effects can enhance patient compliance in both the response phase and the remission phase of treatment. However, as with most SSRIs, including paroxetine, St John's wort is likely an inducer of cytochrome P-450 3A4 and has the potential to cause many drug interactions. Caution must be taken when recommending St John's wort to patients concurrently taking drugs metabolized by this pathway, such as digoxin, warfarin, cyclosporine, and oral contraceptives.

This study had strong internal validity, but whether these results can be generalized to other St John's wort products is less clear. Preparations of St John's wort available on the market might vary considerably in their pharmaceutical quality. One study from 2003 found that only 2 of 54 commonly available St John's wort products in Canada and the United States had observed

concentrations within 10% of the label claim.[10] However, as of January 2006 all natural health products on the Canadian market must comply with Health Canada's Natural Health Products Regulation, resulting in better-quality products through enhanced licensing, manufacturing, and labeling standards.

The product tested in this study, *Hypericum* extract (WS 5570), was a patented extract developed and produced by Dr Willmar Schwabe Pharmaceuticals in Karlsruhe, Germany. In Canada, an identical-strength version of WS 5570 that was investigated in the Szegedi trial is marketed as Perika St John's Wort by Nature's Way. This product is standardized to hyperforin, a constituent within St John's wort that is now thought to be responsible for its mood-balancing effect. These products also ensure the long-term stability of the hyperforin content, which is known to be highly unstable. Most other St John's wort products are standardized to a different constituent known as hypericin, and some contain a standardized amount of hyperforin. However, the stability and amount of the hyperforin content might not be a critical issue considering the most recent meta-analysis examining the effectiveness of various *Hypericum* extracts in depression found that *Hypericum* extracts had effects similar to those of standard antidepressants.[7] Physicians who recommend St John's wort to their patients should advise patients to look for products that provide important information on 1) the total extract (eg, 900 mg) and even standardized constituents (eg, hypericin 0.12%-0.28% or hyperforin 3%-6%), 2) the extraction fluid (eg, methanol 80% or ethanol 60%), and 3) the ratio of raw material to extract (eg, 3:1-6:1).

Physicians should establish a good "working alliance" with their patients, which includes discussing treatment options and considering the patient's preference. A good working alliance between patient and physician has a strong relationship to outcome; it is a strong positive predictive factor of treatment outcome in the psychotherapies, regardless of the specific treatment. Moreover, a strong working alliance is also associated with reduced symptom severity, improved patient functioning, and improved compliance with pharmacotherapy.[2] Therefore, the use of St John's wort in patients who prefer natural medicines over standard antidepressants can lead to better response and remission.

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BOTTOM LINE

- St John's wort (as used in this study) can be at least as effective as paroxetine in acute treatment of moderate to severe depression among adults in the short-term.
- Care must be taken when selecting a St John's wort product.
- Although St John's wort is better tolerated than paroxetine, it is not free of adverse events and has the potential to cause drug interactions.
- This study does not provide information on comparisons of St John's wort and other SSRIs or alternative antidepressants.

POINTS SAILLANTS

- Le millepertuis (tel qu'utilisé dans cette étude) peut être au moins aussi efficace que la paroxétine dans le traitement actif à court terme de la dépression modérée à grave chez les adultes.
- Il faut choisir avec soin le produit à base de millepertuis.
- Même si le millepertuis est mieux toléré que la paroxétine, il n'est pas sans avoir des effets indésirables et peut causer potentiellement des interactions médicamenteuses.
- Cette étude ne donne pas de renseignements comparant le millepertuis avec d'autre ISRS ou antidépresseurs.

References

1. IMS Health Canada. *Top 10 diagnoses in Canada, 2006*. Mississauga, Ont: IMS Health Canada; 2007. Available from: **www.imshealthcanada.com/vgn/images/portal/cit_40000873/43/11/79014602Trends06_En_07CORR.pdf**. Accessed 2007 July 22.
2. Canadian Psychiatric Association. Canadian Network for Mood and Anxiety Treatments. Clinical practice guidelines for the treatment of depressive disorders. *Can J Psychiatry* 2001;46(Suppl 1):5S-90S.
3. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch Gen Psychiatry* 1998;55(7):580-92.
4. MacGillivray S, Arroll B, Hatcher S, Ogston S, Reid I, Sullivan F, et al. Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis. *BMJ* 2003;326(7397):1014.
5. Troppmann L, Johns T, Gray-Donald K. Natural health product use in Canada. *Can J Public Health* 2002;93(6):426-30.
6. Barnes PM, Powell-Griner E, McFann K, Nahin R. Complementary and alternative medicine use among adults: United States, 2002. *Adv Data* 2004;(343):1-19.
7. Linde K, Berner M, Egger M, Mulrow C. St John's wort for depression: meta-analysis of randomised controlled trials. *Br J Psychiatry* 2005;186:99-107.
8. Edwards JG, Anderson I. Systematic review and guide to the selection of selective serotonin reuptake inhibitors. *Drugs* 1999;57(4):507-33.
9. Hypericum Depression Trial Study Group. Effect of *Hypericum perforatum* (St John's wort) in major depressive disorder: a randomized controlled trial. *JAMA* 2002;287(14):1807-14.
10. Draves AH, Walker SE. Analysis of the hypericin and pseudohypericin content of commercially available St John's wort preparations. *Can J Clin Pharmacol* 2003;10(3):114-8.